REMARKS

The Advisory Action mailed March 20, 2002 has been received and reviewed. Claims 1-17 and 19-22 are pending in the application. All claims stand rejected. Applicants propose to amend claims 1 and 19 as set forth herein. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

I. 35 U.S.C. § 112, Second Paragraph

Claim 22 was rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. The rejection was overcome in response to the applicants' amendment filed February 27, 2002.

II. 35 U.S.C. § 103(a)

A. Claims 1-3, 7, 9-11, 19, 20, and 22

Claims 1-3, 7, 9-11, 19, 20, and 22 were rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Dellaporta and Koes et al. Applicants respectfully traverse the rejections.

As an initial matter, applicants respectfully submit that the Examiner's conclusion that "for the purpose of the method, whether amplification is selective or not does not make any difference" is misplaced. (*See*, Advisory Action, page 3). It is essential for the methods of pending claims 1 and 19 that all of the insertion elements flanking any gene be amplified. To clarify that all of the flanking sequences of the pool are amplified, applicants propose to amend independent claims 1 and 19 to include the phrases "each of" and "plurality of" such that the claims recite in part "amplifying each of said plurality of insertion element flanking sequences." The specification discloses that each of the plurality of insertion element flanking sequences is amplified. (*See*, specification, page 15, line 14 to page 16, line 11.)

Applicants reassert that a *prima facie* case of obviousness cannot be established because Dellaporta and Koes et al. do not teach each and every limitation of independent claims 1 and 19. M.P.E.P. § 706.02(j) sets forth the standard for a Section 103(a) rejection:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). (Emphasis added).

Each and every limitation of claims 1 and 19 are not taught or suggested by the prior art references. Specifically, neither Dellaporta nor Koes et al. teach the limitation of amplifying each of the plurality of nucleic acid flanking sequences. Dellaporta discloses "non-selective amplification... which will simultaneously amplify a broad class of insertion junctions," but does not teach amplifying each of the plurality of nucleic acid flanking sequences. (*See*, U.S. Patent 6,013,486, Col. 11, lines 46-50). As further stated in Dellaporta, "it will, of course, be preferred that any such population [used for identifying an insertional mutant] contain a sufficient number of insertion events that there is a reasonable likelihood of detecting at least one insertional mutant from any particular gene or locus." (*See*, *Id.* at Col. 4, lines 14-18). Thus, Dellaporta indicates that not all of the insertional mutants may be amplified. Koes et al. discloses using a transposan- and a gene-specific primer for individual plants with a transposan element that only amplifies the specific gene with the transposan element inserted, but does not teach amplifying each of the plurality of nucleic acid flanking sequences. (*See*, Koes et al. Abstract).

Further, Dellaporta does not teach or suggest a library in a 3D array of block, row and column pools and Koes et al. does not disclose the screening method of the present claims. Since each and every limitation of the presently claimed invention is not taught or suggested by the prior art references, a *prima facie* case of obviousness has not been established. Accordingly, applicants respectfully request reconsideration and withdrawal of the obviousness rejections of claims 1 and 19.

It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). As stated in Dellaporta, mutant identification systems where "transposan-induced mutations are isolated for known gene

sequences by the general strategy known as 'site-selected' mutagenesis... rel[ying] on the power of PCR to amplify a collection of specific junction fragments between an inserted element and a known target gene sequence... have had limited success in applications toward large-scale genomic investigations" and that "the need for individual amplifications of each gene being investigated represents a significant hindrance when seeking to identify more than a small number of insertional mutants." (U.S. Patent 6,013,486, Col. 1, lines 35-41 and lines 54-60). Dellaporta specifically refers to the "site selected" approach of Koes et al. which was "used to identify insertion mutations in Petunia, using the tranposan dTph1 (Koes et al. 1995)." (*Id.* at lines 45-47). Therefore, Dellaporta teaches away from Koes et al. by indicating that the "site selected" approach of Koes et al. represents a significant hindrance that renders the combination of the references improper. Accordingly, applicants respectfully request reconsideration and withdrawal of the obviousness rejections of claims 1 and 19.

Further, there is no suggestion or motivation to combine or modify the teachings of Dellaporta and Koes et al. because the two references have different aims and use different methods. For instance, Koes et al. reduces the complexity of the 3D array by using a gene specific primer, where the gene specific primer may be freely designed to improve the sensitivity of the hydribization of the primer to the one single gene insertion. In comparison, Dellaporta uses primers designed to hydridize to the insertion elements where the sensitivity is determined by the efficiency of the PCR reaction of the amplified gene which cannot be controlled. Dellaporta also differs from Koes et al. in that Dellaporta discloses the preparation of an insertion library where the flanking sequences are amplified simultaneously, while Koes et al. discloses a genomic library where one specific sequence is amplified. Moreover, the flanking element sequences in Dellaporta are unknown while the flanking sequences in Koes et al. are known, allowing for a 3D array to be employed in Koes et al. while searching for a specific sequence in the pool of sequences.

Also, since Koes et al. discloses amplification of a specific sequence, a person skilled in the art would not combine the non-selective amplification methods disclosed in Dellaporta with the selective amplification methods of Koes et al. Based on the teachings of Dellaporta, each amplification event would not be predicted to be amplified with a comparable efficiency because one skilled in the art would expect competition between the different sequences that are to be amplified.

Thus, there is no guarantee in Dellaporta that a given mutation will be detected. As stated in Dellaporta, the random distribution of insertion mutations throughout the target genome "will ...reduce the size of the population needed to have a reasonable probability of detecting any given insertion mutation." (U.S. Patent 6,013,486, Col. 4, lines 25-29). Therefore, a person of ordinary skill in the art would not predict that the screening method of Dellaporta would be able to amplify all insertion events in a complex 3D array with pools of 100 sequences, wherein each of the mutated sequences in the pool would be amplified with a comparable efficiency.

Also, Koes et al. cannot be a particular embodiment of Dellaporta as asserted in the Advisory Action (*See*, Advisory Action, page 3) because Koes et al. was published in 1995 while Dellaporta was filed in 1997. If Koes et al. were an embodiment of Dellaporta, then the Dellaporta patent would not have issued since the embodiment of Koes et al. would have destroyed the novelty of Dellaporta.

These differences suggest that a person of ordinary skill in the art would not have been motivated to combine the teachings of Dellaporta and Koes et al. Accordingly, applicants request reconsideration and withdrawal of the obviousness rejections of claims 1-19.

B. Claim 4

Claim 4 was rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Dellaporta and Koes et al. as applied to claims 1-3, and further in view of Sour et al. Applicants respectfully traverse the rejection.

Claim 4 is patentable at the very least as depending from non-obvious independent claim 1. Accordingly, applicants request reconsideration and withdrawal of the obviousness rejection of claim 4.

C. Claims 5, 6, 8, and 12

Claims 5, 6, 8, and 12 were rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Dellaporta and Koes et al. as applied to claim 1, and further in view of Vos et al. Applicants respectfully traverse the rejections.

Claims 5, 6, 8, and 12 are patentable at the very least as depending, directly or indirectly, from non-obvious independent claim 1. Accordingly, applicants request reconsideration and withdrawal of the obviousness rejections of claims 5, 6, 8, and 12.

D. Claims 13-17 and 21

Claims 13-17 and 21 were rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Dellaporta and Koes et al. as applied to claims 1 and 19. Applicants respectfully traverse the rejections.

Claims 13-17 depend, directly or indirectly, from independent claim 1 and claim 21 depends from claim 19. Claims 13-17 and 21 are patentable at the very least as depending from non-obvious independent claims. Accordingly, applicants request reconsideration and withdrawal of the obviousness rejections of claims 13-17 and 21.

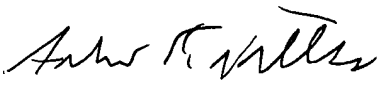
ENTRY OF AMENDMENTS

The proposed amendments to claims should be entered by the Examiner because the amendments are supported by the as-filed specification and drawings and do not add any new matter to the application. Further, the amendments do not raise new issues or require a further search. Finally, if the Examiner determines that the amendments do not place the application in condition for allowance, entry is respectfully requested since they certainly remove issues for appeal.

CONCLUSION

In view of the amendments and remarks presented herein, applicants respectfully submit that the amended claims define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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Date: June 12, 2002

Attachment: Marked up version of the amended claims

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Four times amended) A method for simultaneous screening for one or more gene insertion mutants in a population of any organism comprising:

preparing an insertion element mutant library comprising a plurality of nucleic acid insertion elements and insertion element flanking sequences, said insertion element flanking sequences originating from a defined population of an organism wherein said gene insertion mutants are to be detected and wherein said insertion element library is built in a 3D-array of block, row and column pools;

amplifying each of said plurality of insertion element flanking sequences from said block, row and column pools using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements; and

fixing a set of nucleic acid amplification products representing said insertion element flanking sequences derived from said block, row and column pools to a solid support as target for hybridization.

19. (Four times Amended) A method for parallel simultaneous screening for one or more gene insertion mutants in a population of any organism comprising:

preparing an insertion element mutant library comprising a plurality of nucleic acid insertion elements and insertion element flanking sequences, said insertion element flanking sequences originating from a defined population of an organism wherein said gene insertion mutants are to be detected and wherein said insertion element library is built in a 3D-array of block, row and column pools;

amplifying each of said plurality of insertion element flanking sequences from said insertion element mutant library using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements; and

producing a set of labelled amplification products representing said insertion element flanking sequences derived from said block, row and column pools to use as probes to hybridize to a solid support to which a gene library has been fixed as target(s) for hybridisation, wherein said gene library is organized in at least a two-dimensional array.